Comments on Liver Injury Related to the Use of Acetaminophen

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1.0 INTRODUCTION

The Rocky Mountain Poison and Drug Center of the Denver Health and Hospital Authority has been actively involved in acetaminophen research for 40 years. Several of our published studies address issues highlighted in the meeting notice, but these data were not apparently addressed by the United States Food and Drug Administration (FDA) in the recently released background package for June 29-30, 2009, meeting of the Drug Safety and Risk Management Committee, Anesthetic and Life Support Drugs Advisory Committee and Nonprescription Drugs Advisory Committee. The purpose of this document is to present research data that was not included in the FDA background package. The full text of selected publications are attached.

All studies conducted to date have been investigator-initiated studies. Several of our studies have been funded by McNeil Consumer Healthcare through their investigator-initiated program.

2.0 SAFETY OF ACETAMINOPHEN AT 4 TO 6 GRAMS PER DAY

2.1 PROSPECTIVE TRIALS INDICATE THAT ACETAMINOPHEN IS SAFE AT FULL THERAPEUTIC DOSE IN ADULTS WITH A VARIETY OF COMORBID DISEASES

- **Adult clinical trials reported in Medline or EMBASE for the period 1966-2003 revealed 30,865 subjects that received multiple dose treatment with acetaminophen.** (*Dart RC, et al. Does therapeutic use of acetaminophen cause acute liver failure? Pharmacotherapy 2007; 27(9):1219-1230.)*
  - A total of 129 (0.4%) subjects were reported to have one or more values of serum alanine aminotransferase (ALT) above the upper limits of normal.
  - No cases of hepatic failure or clinically significant liver injury were reported.
    - The reports included 4,263 patients that received 3.9-4.0 grams per day.
    - The mean duration of treatment was 5.5 days.
  - Acetaminophen use was not limited to healthy volunteers. Several studies included patients with concomitant illnesses such as acute stroke, diabetes, advanced cancer of various types, multiple sclerosis, coronary artery bypass grafting, total hip arthroplasty, abdominal surgery, and a variety of surgical procedures requiring general anesthesia.
  - An update of the medical literature review since 2003 is ongoing.

- **A systematic review of pediatric clinical trials reported in MEDLINE or EMBASE for the period 1950 – 2006 showed similar findings.** *(Lavonas EJ, Dart RC. Hepatotoxicity is rare following therapeutic dosing of acetaminophen. Hepatology 2008; 48(4 suppl): 506A.)*
  - 32,307 children received acetaminophen in these trials.

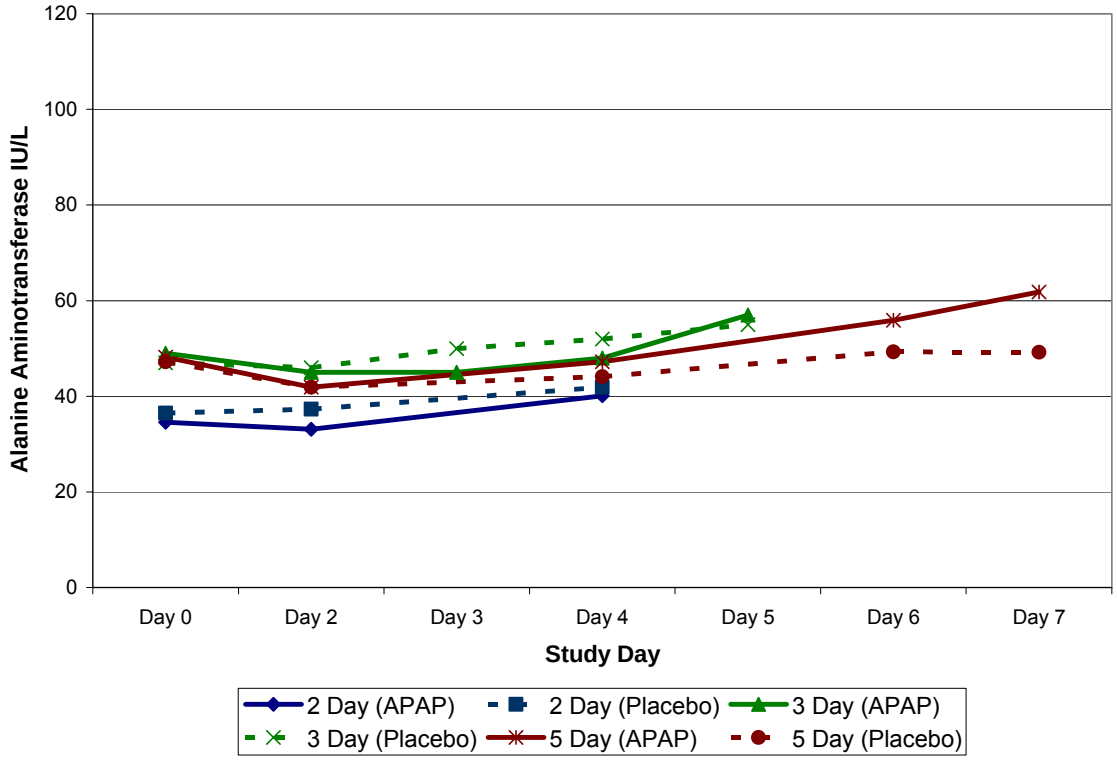
- These trials included children who might be considered at-risk for acetaminophen complications, including children with acute febrile illness, post-operative pain, malaria, premature and newborn infants, and children receiving induction chemotherapy for cancer.
- Transient mild transaminase elevations were rare (7 cases reported; 0.022%).
- No child in these trials developed symptomatic liver toxicity, protime or bilirubin elevation, or permanent sequelae of any kind.

2.2 PROSPECTIVE TRIALS INDICATE THAT ACETAMINOPHEN IS SAFE IN POPULATIONS WITH PUTATIVE HIGH RISK CONDITIONS: ALCOHOLIC LIVER DISEASE AND HEPATITIS C

2.2.1 Alcoholic Liver Disease

- **We have conducted several studies in patient populations suggested to be at higher risk for acetaminophen-related hepatotoxicity (recently abstaining alcoholics, including subjects with alcoholic hepatitis or hepatitis C) and no subject has developed clinical liver injury despite receiving the maximum dose of acetaminophen for up to 5 days (Figure 1).** (*Kuffner EK,et al. Effect of maximal daily doses of acetaminophen on the liver of alcoholic patients. Arch Intern Med 161:2247-2252, 2001; Kuffner EK, et al. The effect of acetaminophen (four grams a day for three consecutive days) on hepatic tests in alcoholic patients – a multicenter randomized study. BMC Medicine 2007;5:13-19; Green JL, et al. Hepatic function in alcoholics throughout 5 days of maximal therapeutic dosing of acetaminophen (APAP). Clinical Toxicology 2005; 43(6):683.)*

Figure 1. Serial Alanine Aminotransferase Activity in Alcoholics Receiving Acetaminophen 4 Grams per Day for 2, 3 and 5 Consecutive Days

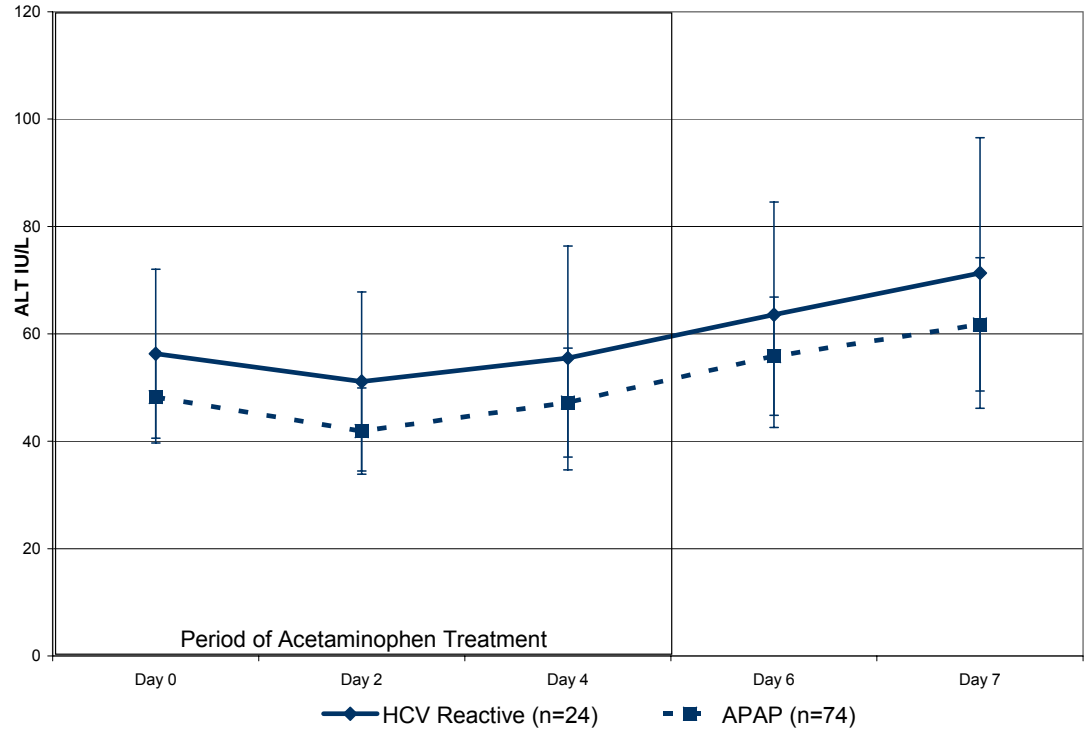


- **Bartels, et al independently confirmed these findings in alcoholic subjects using a more sensitive marker of hepatic injury (Glutathione-s-transferase, GST).** (*Bartels SA, et al. Are recommended doses of acetaminophen hepatotoxic for recently abstinent alcoholics? A randomized trial. Clin Toxicol 2008; 46(3):243-9.)*
  - There was no change in GST or ALT after administration of 4 grams per day of acetaminophen for 4 days.

2.2.2 Hepatitis C

- **Green, et al administered acetaminophen four grams per day to alcoholic subjects for 5 consecutive days: 50 subjects reactive for HCV antibody were included. The pattern of ALT change showed no difference from ALT change compared to all alcoholic patients enrolled (Figure 2).** (*Green JL, et al. Treatment of alcoholic HCV patients with acetaminophen 4 g/day for 5 days does not affect hepatic tests compared to placebo. Hepatology 2007; 46, (4, Suppl 1): 821A.)*

Figure 2. Serial Alanine Aminotransferase in Alcoholic Patients Given Acetaminophen 4 Grams per Day for Five Consecutive Days



- **Our results are consistent with those of Dargere.** (*Dargere S, et al. Lack of toxicity of acetaminophen in patients with chronic hepatitis C: a randomized controlled trial. Gastroenterology 2000;118:A947.)*

2.2.3 Patients with liver cirrhosis

- **Benson studied patients with liver disease in a 14 day crossover trial of acetaminophen 4 grams per day. The results indicated no effect of acetaminophen.** *(Benson GD. Acetaminophen in chronic liver disease. Clin Pharmacol Ther 1983;33:95-101.)*

2.3 PROSPECTIVE TRIALS SUGGEST THAT ACETAMINOPHEN IN DOSES 4 TO 6 GRAMS DAILY ARE SAFE

- **The Paracetamol (Acetaminophen) in Stroke (PAIS) Trial. This randomized placebo-controlled trial administered acetaminophen (6 g daily for 3 consecutive days) to 697 patients with ischemic stroke or intracerebral hemorrhage.** (*den Hertog H, et al. The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial. Lancet Neurol 2009; 8(5):434-40.)*
  - Comorbid conditions were common (hypertension 49%, diabetes 14%, hypercholesterolemia 24%, and peripheral vascular disease 9%).

- Stroke outcome was improved in the group receiving acetaminophen.
- Adverse events were similar in both groups. “In particular, there was no increased rate of infections or liver enzyme disturbances in patients treated with paracetamol.”
- Liver failure did not occur in either the placebo or acetaminophen groups.

❖ **Dippel, et al administered acetaminophen (4 grams or 6 grams daily for 5 days) to 51 patients following acute ischemic stroke.** *(Dippel DW et al. Effect of paracetamol (acetaminophen) on body temperature in acute ischemic stroke: a double-blind, randomized phase II clinical trial. Stroke. 2001 Jul; 32(7):1607-12.)*

- Stroke outcome was improved in the 6 grams per day, but not the 4 grams per day group.
- Liver function disturbance occurred in 23% of patients receiving acetaminophen and 33% of patients receiving placebo. Serious hepatic injury was not reported.

❖ **Dippel, et al administered acetaminophen (6 grams daily for 5 days) to patients with acute ischemic stroke.** *(Dippel DW, et al. Effect of paracetamol (acetaminophen) and ibuprofen on body temperature in acute ischemic stroke PISA, a phase II double-blind, randomized, placebo-controlled trial. BMC Cardiovascular Disorders. 2003 Feb 6; 3(1):2.)*

- Stroke outcome was improved in the acetaminophen group.
- The incidence of liver function disturbances was the same in the ibuprofen and acetaminophen groups. Serious hepatic injury was not reported.

❖ **Gelotte, et al administered acetaminophen 4, 6, or 8 grams per day for 3 consecutive days to 12 healthy volunteers.** *(Gelotte CK, et al. Clinical features of a repeat-dose multiple-day pharmacokinetics trial of acetaminophen at 4, 6, and 8 g/day. Journal of Toxicology - Clinical Toxicology. 2003; 41(5):726.)*

- Results of all liver function tests for all 3 groups and for placebo were within normal limits for the duration of the study.

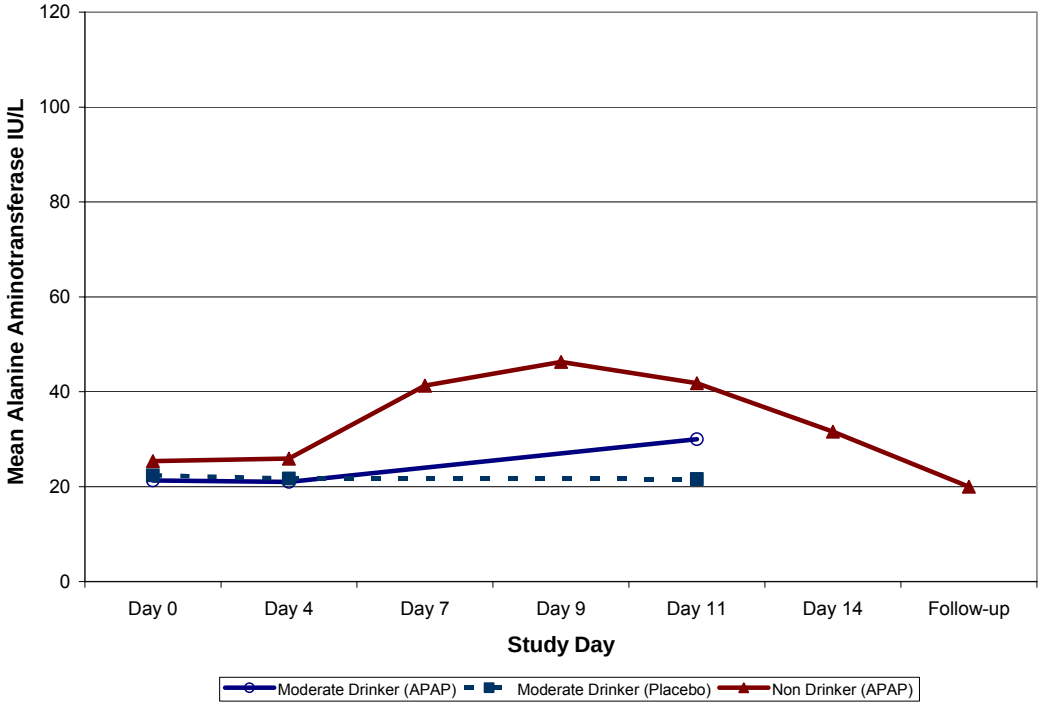
❖ **Several other small trials with similar results have been reported.** *(Boardman PL, et al. Clinical measurement of the anti-inflammatory effects of salicylates in rheumatoid arthritis. BMJ. 1967 Nov 4; 4(574):264-8; Solomon L, et al. Orudis in the management of osteo-arthritis of the knee. A double-blind trial. South African Medical Journal. 1974 Jul 27; 48(36):1526-9; Solomon L, et al. Bumadizone calcium in the treatment of rheumatoid arthritis. South African Medical Journal. 1977 Aug 27; 52(10):391-3.; Stockler M, et al. Acetaminophen (paracetamol) improves pain and well-being in people with advanced cancer already receiving a strong opioid regimen: a randomized, double-blind, placebo-controlled cross-over trial. J Clin Oncol. 2004; 22(16):3389-3394.)*

2.4 THERAPEUTIC DOSES OF ACETAMINOPHEN CAUSE TRANSIENT ALT ELEVATIONS WITHOUT EVIDENCE OF CLINICAL LIVER INJURY

- **Watkins, et al reported that 76% of normal subjects taking 4 grams of acetaminophen daily for 14 days, either alone or in combination with an opioid, developed a serum ALT above the ULN (40 IU/L).** (*Watkins, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA 2006; 296:87-93.)*
  - These ALT elevations were not accompanied by any symptoms or signs of liver dysfunction such as elevation of the INR, increase in the serum bilirubin or decrease in the serum albumin.

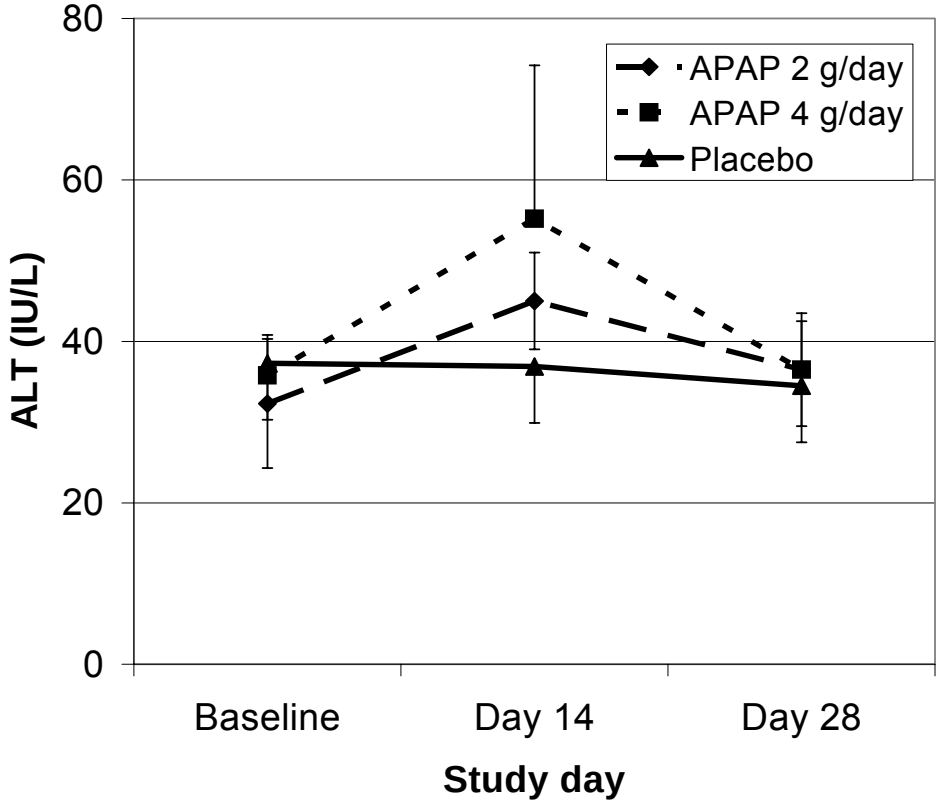
- **Heard, et al found ALT elevations in 20% of moderate drinkers (n=100) and 58% of non-drinkers (n=24) treated with 4 grams per day of acetaminophen for 10 days (Figure 3).** *(Heard K, et al. A randomized trial to determine the change in ALT during 10 days of paracetamol (acetaminophen) administration in subjects who consume moderate amounts of alcohol. Alimentary Pharmacology & Therapeutics 2007; 26(2):283-90; Grazi L, et al. Transient alanine aminotransferase (ALT) elevations in alcohol abstaining subjects with 10 consecutive days of therapeutic acetaminophen (APAP) use. Clinical Toxicology 2008; 46(7):632-3.)*
  - ALT elevations were not accompanied by any symptoms or signs of liver dysfunction (such as elevation of the INR, increase in the serum bilirubin or decrease in the serum albumin).

Figure 3. Serial Alanine Aminotransferase in Moderate Drinkers and NonDrinkers Receiving Acetaminophen 4 Grams per Day for 10 Consecutive Days



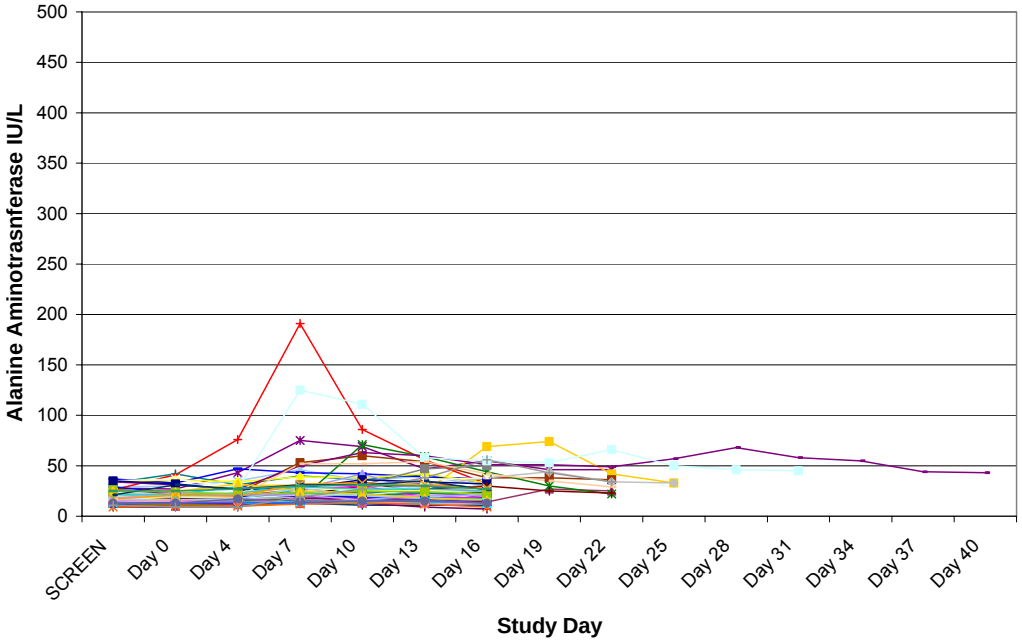
- **Parra, et al reported resolution of ALT elevations while patients remained under treatment with acetaminophen 2 grams or 4 grams for 28 days (Figure 4).** (*Parra, et al. The effect of acetaminophen on the international normalized ratio in patients stabilized on warfarin therapy. Pharmacotherapy. 2007; 27(5):675-68.)*

Figure 4. Serial Alanine Aminotransferase Activity in Patients Treated with Acetaminophen 2 and 4 Grams per Day



- **Heard, et al is currently performing a double-blinded placebo-controlled trial describing the changes in ALT during prolonged dosing of acetaminophen (Figure 5).** *(Heard K, et al. Protocol title "Aminotransferase Trends During Prolonged Therapeutic Acetaminophen Dosing", NCT00743093, IND 78,042, unpublished data.)*
  - Subjects are treated with 4 grams per day of acetaminophen (or placebo) for a minimum of 16 days. At day 16, subjects are stopped if their serum ALT is below the upper limit of normal for our laboratory and within 10 units of their baseline ALT. If these criteria are not met at Day 16, the subject is continued on treatment until they have two consecutive ALT values within normal.
  - Randomized 4:1 acetaminophen to placebo. Serum ALT and other markers of liver injury are measured every 3 days.
  - The results from the first 81 completed subjects (both acetaminophen 4 grams per day and placebo) indicate that ALT activity increases and then decreases while the subject is still on acetaminophen treatment (Figure 5).

Figure 5. Serial Alanine Aminotransferase Activity in Healthy Volunteers Receiving Acetaminophen 4 Grams per Day or Placebo



- **The draft FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation has recognized that asymptomatic ALT elevations generally resolve on therapy and now recommends continuing treatment in subjects who have ALT elevation less than 8x the upper limit of normal as long as there are no symptoms of liver disease or elevation of the INR or bilirubin.** (*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072278.pdf*)

- **Asymptomatic ALT elevation has been described with other medications such as isoniazid** (*Nolan CM, et al. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA. 1999 Mar 17; 281(11):1014-8.*)**, statins** (*Charles EC, et al. Evaluation of cases of severe statin-related transaminitis within a large health maintenance organization. Am J Med 2005; 118(6):618-24.*) **and tacrine** (*Watkins P, et al. Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. JAMA 1994; 271(13):992-8.)*
  - Typically, when ALT elevation occurs with these medications, it resolves when the therapy is continued.

3.0 PROTEIN ADDUCTS

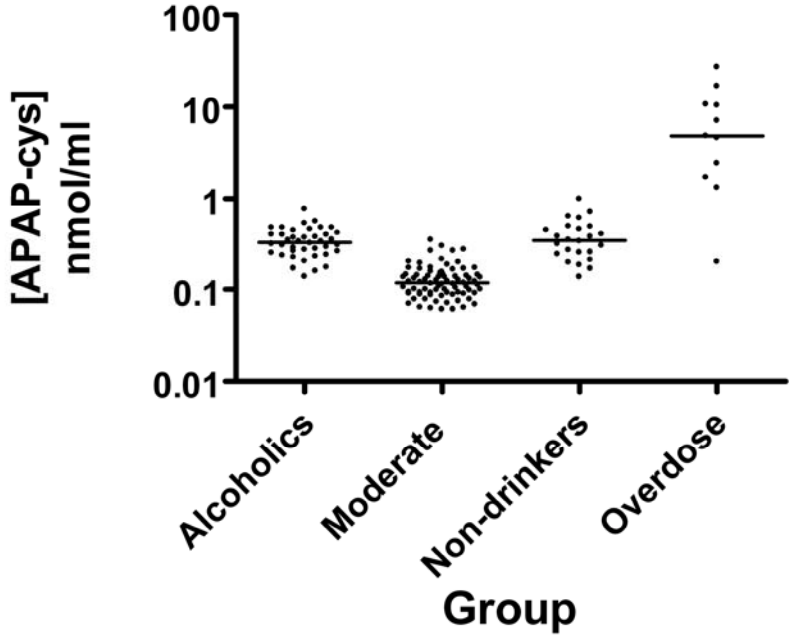
3.1 PROTEIN ADDUCTS INDICATE METABOLISM OF ACETAMINOPHEN RATHER THAN EVIDENCE OF LIVER INJURY

- Acetaminophen-cysteine adducts are formed when the toxic metabolite of acetaminophen (NAPQI) is not detoxified by glutathione and binds to cysteine residues in cellular proteins.

- **Detection of serum acetaminophen adducts are proposed as a marker of acetaminophen-induced liver injury.** *(Davern TJ, et al. Measurement of serum acetaminophen-protein adducts in patients with acute liver failure. Gastroenterology 2006; 130:(3)687-94.)*

- **A group of studies demonstrates that protein adducts of acetaminophen are formed with acetaminophen 4 grams per day in alcoholics, moderate ethanol users and non-drinkers without evidence of clinical liver injury (Figure 6).** ***(Heard K, et al. Serum acetaminophen-cysteine adducts: a comparison of concentrations during therapeutic dosing and overdose. Hepatology 2008; 48:471A).***
  - In the group of subjects receiving acetaminophen 4 grams per day, the serum acetaminophen-cysteine concentration is not correlated with the serum ALT. This further suggests that at therapeutic doses, the formation of adducts alone is not evidence of toxicity.

Figure 6. Acetaminophen Protein Adducts Following Acetaminophen 4 Grams per Day and Acetaminophen Overdose



4.0 PACK SIZE LIMITS DO NOT EFFECTIVELY REDUCE ACETAMINOPHEN POISONING

- **An article by Professor N. Bateman, Director of the Edinburgh Poison Information Service, reviews the numerous articles written on the issue of pack size limitation in the United Kingdom.** (*Bateman N,et al. Limiting paracetamol pack size: has it worked in the UK? Clinical Toxicology; in press.*)
  - In 1998, England, Scotland, and Wales restricted acetaminophen sales to 32 tablets per transaction in pharmacies and 16 tablets in other retail outlets, with a maximum strength of 500 mg per tablet.
  - Suicide rates began to decline before the pack size restriction was implemented.
  - There has been no decrease in the number of patients taking large overdoses (100 tablets or more), nor in the mean 4-hour plasma acetaminophen concentration measured in acetaminophen overdose victims.
  - Acetaminophen-related overdose admission rates, liver unit admissions, and liver transplantations in the UK all decreased in parallel with the corresponding rates related to overdoses of other medications, and in parallel with declining rates of suicide overall.
  - In contrast to pack size limitations, the withdrawal of propoxyphene-acetaminophen combination products in 2005 seems to be responsible for the greatest reduction in deaths occurring in association with acetaminophen ingestion.

5.0 SUMMARY

- Acetaminophen 4 grams per day is safe, even in putative vulnerable populations.
- Asymptomatic ALT elevations observed with therapeutic doses of acetaminophen are very unlikely to progress to clinically significant liver injury.
- Acetaminophen-cysteine adducts are a marker of acetaminophen exposure but are not definitive evidence of acetaminophen toxicity.
- The data regarding pack size limits imposed in the UK are contradictory. At best, this major intervention had a limited effect on acetaminophen poisonings or death associated with acetaminophen ingestion.